PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
11B2046.WO8		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IT 03/00401	27.06.2003	27.06.2003
International Patent Classification (IPC) or both national classification and IPC		
A61K9/14		
Applicant		
BIOPROGRESS S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.05.2004	13.10.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT 03/00401

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12 as originally filed

Claims, Numbers

1-16 filed with telefax on 14.06.2005

Drawings, Sheets

1/7-7/7 filed with telefax on 28.09.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	12-16
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	12-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents :

D1: DE 199 29 361 , disclosing how an active principle is incorporated into a PVP-VA melt (solid solution) and then coground to a powder/granulate;
D2: WO 01/68100 A, disclosing torasemide preparations: the active principle is incorporated into a NVP-VA (N-vinylpyrrolidone-vinylacetate copolymer) melt and then coground to a powder/granulate
D3: US 6 322 816 B, disclosing ibuprofen in a porous polymer matrix; as a suitable embodiment a copolymer NVP-VA is indicated.
D4: US 5 741 519 B, disclosing a solid solution of the active principle in a NVP/VA matrix
D5: GB 1 560 406 A

Unless otherwise indicated, reference is made to the relevant passages emphasized in the International Search Report.

The subject-matter of the composition and use claims 12-16 appear to lack novelty under Art. 33(1) and (2) PCT over D1-D2. In fact, albeit the process as claimed in claims 1-15 appears to be novel over the cited prior art, the skilled person would not be able to distinguish the final product from the one obtained with the prior art processes or a composition thereof with exactly the same ingredients (active principle and NVP/VA).

The closest prior art is D1 or D2; the difference is the process for obtaining the mixture active/polymer; the problem would then be how to obtain provide an improved process for enhancing drug solubility. the skilled person would not move from a comelting, extrusion and grinding to a simple cogrinding in powder form, i.e. to a less thorough mixing of the ingredients. Hence, and in view of thr good results reported in the application, the method claims 1-11 appear to be inventive as required by Art. 33(1) and (3) PCT.

AMENDED CLAIMS

1. Method for preparing a composite product comprising a step in which an active substance in powder form undergoes co-grinding with a carrier comprising N-vinyl-2-pyrrolidone/vinyl acetate copolymer in powder form.

2. Method according to claim 1, in which the carrier is N-vinyl-2-pyrrolidone/vinyl acetate.

3. Method according to claim 1, in which the co-grinding step takes place in dry conditions.

4. Method according to claim 1, in which the active substance is chosen among non steroidal anti-inflammatory agents.

5. Method according to claim 1, in which the active substance is chosen among anti-hypertensives.

6. Method according to claim 1, in which the active substance is chosen among hepato-biliary agents.

7. Method according to claim 1, in which the active substance is chosen among substances that are scarcely soluble in water environment.

8. Method according to claim 7, in which the active substance is chosen among scarcely water soluble substances having a low dissolution speed.

9. Method according to at least one of the preceding claims, in which the active substance is chosen among: anti-inflammatory agents, analgesics, relaxants, anti-microbic agents, antiseptics, acid pump inhibitors, H_2 antagonists, anti-emetics and anti-nausea, biliary acids, oral hypoglycemizers, diuretics, anti-hypertensives, sulfonamides, ace-inhibitors, hypolipemizers, anti-mycotic agents, antihistamines, hormones, quinolone derivates, antibacterial agents, beta-lactame and fluoroquinolone antibiotics, antiviral agents, anti-neoplastic agents, immuno-

modulators and immuno-suppressors, anti-gout agents, anesthetics, analgesics, antipyretics, $5HT_1$ agonists, anti-Parkinson agents, anti-psychotic agents, tranquillizers, antidepressants, anti-parasitic agents, non-cortisone anti-allergic agents, anti-asthmatic agents, anti-glaucoma agents, inhibitors of carbonic anhydrase or beta-blockers.

10. Method according to claim 9, in which the active substance is chosen among: paracetamol, nifedipine, piroxicam, ibuprofen, sulindac, diclofenac, alclofenac, ketorolac, indomethacine, naproxen, fenoprofen, flurbiprofen, ketoprofen, cimetidine, ranitidine, mesalazine, ursodeoxycholic acid, mefenamic acid, sinvastatin, megestrol acetate, lorazepam, diazepam, cyclosporin, ubiquinone, tolbutamide, ketanserine, furosemide, nicergoline, losartan, econazole, miconazole, taxol, progesterone, prednisolone, beclometasone, nalidixic acid, finasteride, ciprofloxacine, ofloxacine, lomefloxacine, methotrexate, etoposide, daunorubicine, tamoxifen, allopurinol, clodronic acid, sumatriptan, carbamazepine, clorpromazine, clozapine, sulpiride, buspirone, fluoxetine, citalopram, caffeine, metronidazole, acetazolamide.

11. Method according to at least one of the preceding claims, in which the active substance and N-vinyl-2-pyrrolidone/vinyl acetate copolymer are present in a weight ratio between 1:200 and 10:1; preferably between 1:100 and 5:1.

12. Composite product that can be obtained from a process according to at least one of the claims 1 to 11.

13. Pharmaceutical composition comprising the composite product according to claim 12.

14. Pharmaceutical composition according to claim 13, in which the pharmaceutical form is chosen among: tablet, capsule, pellet, syrup and solution.

15. Method for preparing the pharmaceutical composition according to claim 13 comprising a step in which the composite product according to claim 12 is mixed with excipients or pharmaceutically acceptable additives.

~~16. Use of an active substance and of a carrier comprising N-vinyl-2-pyrrolidone/vinyl acetate for preparing a pharmaceutical formulation.~~

16. Use of the composite product according to claim 12 for preparing a pharmaceutical formulation.

TABLE 1

Carrier	Example	Nimesulide / Carrier Ratio	Conservation conditions									
			Beginning of stability		*15 days in packet and then 25 days at 4°C in closed vial*		*15 days in packet and then 25 days in open vial*		*40 days in packet*		*60 days in packet at room T and RH*	
			ΔH_f (mJ/mg)	T_f(°C)	ΔH_f (mJ/mg)	T_f(°C)	ΔH_f (mJ/mg)	T_f(°C)	ΔH_f (mJ/mg)	T_f(°C)	ΔH_f (mJ/mg)	T_f(°C)
NVP/VA	1	1/3	20.4	107.0	4.4	107.8	0	0.	0	0	12.1	108.5
	2	1/4	10.2	105.0	0	0	0	0	0	0	2.1	105.9
PVP	A	1/3	22.8	121.9	18.9	117.6	19.0	123.4	22.5	119.7	18.3	123.6
	B	1/4	22.0	119.2	18.2	119.2	16.8	122.4	10.4	118.9	10.7	120.4
PVP-CL	C	1/3	21.0	130.0	25.9	132.8	22.5	131.7	21.7	131.9	28.4	131.5
	D	1/4	21.0	128.2	19.9	132.0	20.6	131.2	18.6	131.1	15.1	129.3

TABLE 2

Carrier	Example	Nimesulide / Carrier Ratio	Activation time (hours)					
			0		*1*		*2*	
			ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)
NVP/VA	3	1/3	60.6	137.3	34.7	114.9	26.0	108.5
	4	1/4	59.6	140.2	19.0	109.4	10.6	107.7
PVP	E	1/3	95.8	149.8	28.5	136.0	21.0	135.4
	F	1/4	75.9	149.4	15.0	133.0	15.1	130.5
PVP-CL	G	1/3	79.2	150.7	32.9	132.6	31.2	132.0
	H	1/4	77.2	150.5	24.6	130.6	23.7	129.6

TABLE 3

Carrier	Example	Activation time (hours)											
		0		1		2		3		4			
		ΔH_c (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)		
-	-	107.7	204.7	-	-	-	-	-	-	-	-		
NVP/VA	5	-	-	45.8	147.1	45.8	140.0	39.2	144.4	29.0	142.1		
PVP-CL	I	-	-	63.2	200.0	47.5	199.5	35.5	201.3	34.3	199.4		
β-ciclodestrin	L	-	-	62.3	177.9	64.9	177.5	56.6	177.8	54.5	176.9		

TABLE 4

Carrier	Example	Activation time (hours)											
		0		1		2		3		4			
		ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)		
-	-	105.5	174.3	-	-	-	-	-	-	-	-		
NVP/VA	6	-	-	31.5	128.9	17.8	125.4	17.6	124.1	15.8	128.3		
PVP	M	-	-	45.6	153.0	41.2	152.2	34.7	151.7	33.7	151.7		

TABLE 5

Carrier	Example	UDCA/ Carrier Ratio	Time (hours)									
			0		*1*		*2*		*3*		*4*	
			ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)	ΔH_f (mJ/mg)	T_f (°C)
NVP/VA	7	1/4	20.3	206.2	22.2	143.1	20.5	141.6	14.9	137.9	10.4	137.7
	8	1/5	24.2	206.2	20.7	140.1	16.3	139.1	9.2	138.2	5.8	135.5
β-cyclodextrin	N	1/4	81.1	207.5	40.2	202.5	5.7	201.5	4.2	203.5	7.9	204.8
	O	1/5	84.1	207.5	37.4	203.0	13.3	205.8	5.7	207.3	5.9	201.1

TABLE 6

Carrier	Example	Time (minutes)		
		5	10	15
NVP/VA	2	93.2 %	97.1 %	98.6 %
PVP	B	79.7 %	93.1 %	95.6 %
PVP-CL	D	40.6 %	65.2 %	75.8 %

TABLE 7

Carrier	Example	Time (minutes)				
		2	4	6	8	10
NVP/VA	5	49.3 %	90.4 %	95.2 %	97.6 %	98.7 %
PVP-CL	I	45.4 %	63.2 %	75.5 %	84.4 %	90.5 %